MEDICAL PROCEEDINGS

MEDIESE BYDRAES

A South African Journal for the Advancement of Medical Science

'n Suid-Afrikaanse Tydskrif vir die Bevordering van die Geneeskunde

P.O. Box 1010 · Johannesburg | Posbus 1010 · Johannesburg

Editor : Redakteur

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Vol. 6 | 21 Mei 1960 May 21 | No. 10

REDAKSIONEEL · EDITORIAL

OPERASIE JANUS

NUWE HARTE VIR OUES?

Elders in hierdie uitgawe doen Terblanche, Cywes en Barnard, van die Chirurgiese Afdeling van die Universiteit van Kaapstad, verslag oor 'n herhaling van die merkwaardige Sowjet-eksperiment om die kop van een hond op die lyf van 'n ander oor te plant. In hierdie besondere geval is die tweekoppige chirurgiese skepping toegelaat om ten minste 24 uur lank te leef. (Ons verneem dat in die Russiese geval 29 dae verstryk het voordat die proefneming beëindig is). Dit het geskyn asof die skenker-kop in staat was om normale fisiologiese funksies uit te voer. Dit het, byvoorbeeld, aangebode melk opgelek. Dit laat interessante bespiegelinge ontstaan oor hoër serebrale funksies, insluitende probleme wat met geheue en bekwaamheid geassosieer is. Sal die oorplanting van 'n Einstein-brein 'n menigte begaafdhede met hom saambring?

Die Kaapstadse prestasie is belangrik omdat dit gedemonstreer het dat daar geen chirurgiese struikelblokke is in die weg van ingewikkelde oorplantingsprosedures waarby die oorlewing van so 'n komplekse en delikate orgaan soos die brein betrokke is nie. Dit is 'n noodsaaklike en eerste stap tot die oplossing van wat fundamenteel 'n immunologiese probleem is, nl. die behoud van die skenker-oorplanting deur die draer. Die skrynwerk van die prosedure is vervolmaak. Al wat oorbly is om die immunologiese spykers te smee om die oorplanting stewig vas te hom, en die verwerping daarvan deur die draer te voorkom.

OPERATION JANUS

NEW HEARTS FOR OLD?

Elsewhere in this issue Terblanche, Cywes and Barnard, from the Department of Surgery, University of Cape Town, repeat the remarkable Soviet experiment in which the head of one dog was grafted on to the body of another. In this case the two-headed surgical creation was allowed to survive for at least 24 hours. (In the Russian case we understand that 29 days elapsed before the experiment was terminated). The donor head appeared capable of normal physiological function. For example, it lapped milk when this was offered. This raises interesting speculation about higher cerebral functions including problems associated with memory and ability. Will the transplantation of an Einsteinian brain carry with it its multitudes of talents?

The Cape Town achievement is important in its demonstration that there is no surgical bar to intricate grafting procedures involving the survival of such a complex and delicate organ as the brain. This is a necessary and first step in the solution of what is fundamentally an immunological problem, viz. the retention of the donor graft by the host. The carpentry of the procedure has been perfected. All that remains is to forge the immunological nails which will hold the graft securely enough to prevent its rejection by the host.

It is not clear, from the information so far available, whether the Soviet scientists have made a break-through on this immunological front; but this is obviously the next stage

Uit die inligting wat tot dusver beskikbaar gestel is, is dit nie duidelik of die Sowjet-wetenskaplikes reeds aan hierdie immunologiese front deurgebreek het nie, maar so 'n deurbraak is heel duidelik die volgende stadium, en sal ongetwyfeld die brandpunt van intensiewe biologiese ondersoek word.

Hierdie merkwaardige chirurgiese prestasie het interessante implikasies. As die biologiese probleem eenmaal opgelos is, sal die vernuf en vindingrykheid van die chirurg die enigste faktore wees wat orgaanoorplanting aan bande lê. Trouens, as ons 'n tydperk binnegaan waar brein, hart, niere, ledemate, ens., met immunologiese straffeloosheid oorgeplant kan word, sal die bron van skenker-materiaal ons probleem word. In die geval van minder ingewikkelde situasies, soos bloedvate, buise, ens., sal ons miskien op lewelose sintetiese materiaal kan staatmaak, en bes moontlik sal fisioloë hulle toelê op die ontwikkeling van kunsniere wat die slagoffer van, sê nou maar, chroniese nierontsteking, op of in sy liggaam sal kan ronddra. Voorlopig, egter, sal die brein waarskynlik nog steeds 'n probleem oplewer, maar ook op hierdie besondere gebied maak die sibernetika-deskundiges goeie vordering.

Is ons in sig van die dag wanneer chirurge in staat sal wees om 'n soort Josefskleed bestaande uit talle verskillende dele te maak, wanneer defekte harte en hoofde hernieu sal kan word, en ons uiteindelik 'n soort onsterflikheid op aarde sal bereik? which will be the focus of intensive biological investigation.

This remarkable surgical achievement has interesting implications. Once the biological problem has been solved, the only limitations on organ grafting will be the skill and ingenuity of the surgeon. Indeed, if we enter an era when brains, hearts, kidneys, limbs, etc. can be transposed with immunological impunity, our problem will be the source of donor material. In less complicated situations, such as blood vessels, ducts, etc., we may be able to rely on inert synthetic materials, and no doubt physiologists will press on with the development of artificial kidneys which the victim of, say, chronic nephritis may be able to wear on or in his person. For the time being, however, the brain may still provide a problem, but even here the cyberneticists are forging ahead.

Are we in sight of the day when surgeons can sew a kind of Joseph's coat of many different parts, when failing hearts and heads can be renewed, and a kind of immortality on earth can ultimately be achieved?

TISSUE TRANSPLANTATION IN THE FORM OF HEAD GRAFTING

A PRELIMINARY REPORT

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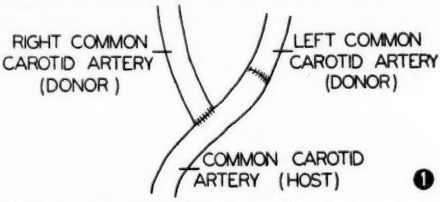
It is no exaggeration to say that surgery would enter a new dimension of accomplishment if tissues could be transplanted with the same freedom between two different individuals as between one part and another of the same individual. The question that immediately comes to mind is whether the homograft problem is soluble in a surgically effective sense. Considering all aspects, this seems reasonably likely. The phenomenon of tolerance, and the existence of a phenomenon of 'enhancement' in its various forms, show that adult animals are by no means as impregnable as we were formerly inclined to believe. When one studies the history of transplantation, one realizes that there is nothing to suggest that the problems will yield to anything but careful experimentation.

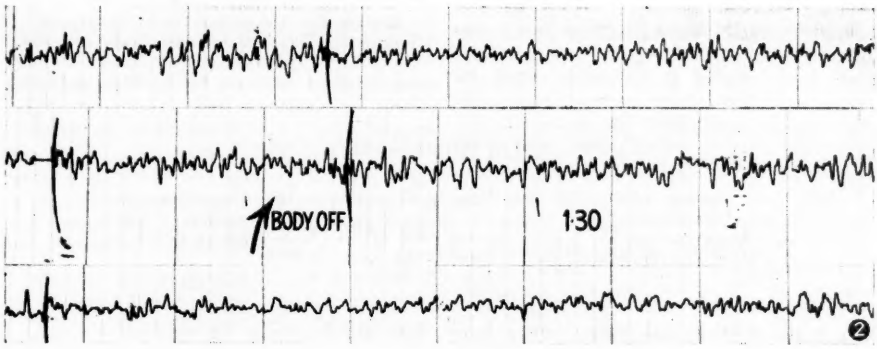
It is not within the scope of this article to discuss the numerous problems of tissue rejection, but we would like to show that homotransplantation in the form of an animal's head is technically possible. Once such a homograft is performed with an adequate blood supply to both heads, the donor head should survive and react normally until rejected by the host's tissue immunological responses. The validity of this statement is shown by the following experimental work.

METHOD

For the success of such a procedure, it is important that, during transplantation, an adequate blood supply be maintained to the donor head throughout without embarrassing the cerebral circulation of the host at any stage.

Two mongrel dogs were anaesthetized with intravenous Pentothal and placed side by side on the operating table. It was found better to use a small donor dog and a large host dog. By means of a collar-incision, both carotid arteries and jugular veins were exposed in the donor and the host.





As long as the principle of an adequate circulation is borne in mind, it is unimportant whether the vascular anastomoses are made end-to-end or end-to-side. The procedure is simplified by the fact that the blood supply of one common carotid and one jugular vein can be interrupted in a dog without affecting cerebral function. Thus one common carotid of the host can be used as the source of supply to both common carotids of the donor, by effecting an end-to-end or an end-to-side anastomosis, as shown in Fig. 1. Similarly, one jugular vein of the host may be used to drain both jugulars of the donor.

To assess the cerebral circulation during the procedure, we utilized a continuous electroencephalographic recording taken from the donor's head. A tracing taken during one experiment is shown in Fig. 2. It is clear that at no stage during the operation was cerebral function seriously affected.

Once the vascular anastomoses were completed, the head was detached, care being taken to control the bleeding from the vertebral vessels and to prevent the continuous escape of cerebral spinal fluid, by closing the open end of the spinal canal with a muscle flap. The muscles and skin of the donor's head were then sutured to the neck of the host in such a way as not to interfere with the blood supply, and the trachea and the oesophagus of the donor were brought out and sutured to the skin on the side of its neck, in order to study the functions of breathing and swallowing afterwards.

RESULTS

All such experiments performed in our laboratories to date have been successful (Fig. 3). In the immediate post-operative period

both the host and the donor head reacted somewhat sluggishly, but this improved rapidly within the next few hours. Within 24 hours the 'animal' reacted normally as ascertained by tests performed. The cerebral and cranial functions of both heads were normal. For example, both heads were observed to lap milk when this was offered.

CONCLUSIONS

These experiments indicate that the technical problems in the grafting of organs, even a head, are not insurmountable. The fact that the head has easily tested functions and tissues very susceptible to the interruption of the blood supply, makes it a suitable organ for ascertaining the technical difficulties which arise in homotransplantation. In addition, we are investigating the immunological responses that follow on such grafts, and these will be the subject of a later report.

There is little doubt that tissue transplantation in various forms will be a real clinical entity in the not too distant future, opening new fields in medicine and surgery.

We wish to express our appreciation and thanks to Prof. J. H. Louw of the Department of Surgery, University of Cape Town, for his encouragement, and to the technical staff of the Marais Laboratory, Mr. C. C. Goosen, Mrs. V. M. Connell and Mr. C. J. Lockett, for their assistance.

We are also indebted to the J. S. Marais, C. L. Herman and Fourcade bequests through the University of Cape Town, and to the Council for Scientific and Industrial Research, for financial assistance.

LIVE POLIOVIRUS VACCINE*

'The past year [1958] may truly be referred to as the international live poliovirus vaccine year, since never before have investigators from so many different parts of the world combined their efforts and facilities to obtain an answer to a question of international public health importance.'

Albert Sabin.[1]

Millions of children and young adults have been vaccinated against poliomyelitis in recent years by means of formalin-inactivated poliovirus—the Salk vaccine—administered subcutaneously. Under the action of the formalin the virus loses its infective properties and ability to multiply, but retains a capacity to stimulate antibody formation in the organism and therefore to confer protection against the disease. This protection has proved satisfactory, since in numerous countries where large groups of the population have been vaccinated, it has lessened the number of paralytic cases. However, its efficacy is probably of limited duration and might not be enough to ensure the general protection of the population at risk in a serious epidemic.

An ideal vaccination should confer the same degree of immunity as is given by the natural disease but without producing untoward side effects. Vaccinations against smallpox and yellow fever are the stock examples of effective protection against virus diseases with risks reduced to a minimum. Researchers have accordingly, for several years past, aimed at producing a poliovirus vaccine which, unlike the formalinized product, would be living and which would multiply in the organism, stimulate the formation of antibodies, and confer protection to the same degree as a natural infection.

By selection of the plaques produced by virus colonies on tissue cultures, the viruses with the most attenuated paralytogenic properties were sought, so that no danger would be involved for those vaccinated. A vaccine of this kind has the advantage of being administered orally and thus of being more convenient for systematic mass immunization.

The virus of poliomyelitis is one of those enteroviruses of which more and more are being discovered, some being recognized as pathogenic, though the disease-causing role of others is still uncertain. Paralytogenic polioviruses are able to invade the central nervous system, and by their pathogenic effect on the cells to bring about various degrees of paralysis. The virus multiplies in various parts of the body—Peyer's patches, the tonsillopharyngeal tissue or the lymph glands—although this does not determine the site of the visible lesions. Viraemia may be more or less marked, and its role in infection and immunity is still a moot point.

Live poliovirus vaccine taken orally, in liquid form or as capsules containing liquid, passes into the intestines, develops there, and is then excreted in the stools and possibly

* With acknowledgments to the *Chronicle of the World Health Organization,* April 1960.

in the pharyngeal secretions. In communities where children live in close contact, these excreted viruses will pass from one child to another, and a phenomenon unique in the history of vaccination can then be observed —a natural 'serial' immunization spreading from *one* vaccinated child to *several* other children. This would be an undoubted advantage if one could be certain that the vaccine viruses will remain attenuated, i.e. that, after passing into the intestines and no longer being subject to human control, they will not regain virulence and become dangerous pathogenic agents at large in the population.

The fear that this might happen was voiced after studies in various countries had indicated that the viruses excreted by vaccinated persons were of a higher degree of neurovirulence for monkeys than was the vaccine virus. However, the authors reported no evidence of progressive increase in neurovirulence for monkeys during prolonged multiplication in the vaccinated individual or after serial passage of virus in human beings.

How can we be certain of the stability of the vaccine viruses? How can we distinguish in the laboratory between the vaccine virus and the various enteroviruses or possible variants of the original virus? How can we assess the degree of protection conferred? What is the role of the other enteroviruses, and what happens when they co-exist in the intestines or tissues with the poliomyelitis vaccine virus? To answer these questions, exchange experiences and compare results, a group of eminent specialists, i.e. those who 'created' the attenuated vaccine, tested it, and took the responsibility of using it in practice, met at the First International Conference on Live Poliovirus Vaccines, held in Washington, D.C., from 22 to 26 June 1959, under the auspices of the Pan American Sanitary Bureau, the World Health Organization and the Sister Elizabeth Kenny Foundation.

The detailed report on these discussions and an account of some 20 vaccination campaigns in 15 countries have just been published in a volume entitled *Live Poliovirus Vaccines*.[2] In addition, a newly published issue of the *Bulletin of the World Health Organization* contains several important articles on live poliomyelitis vaccines and, in particular, accounts of certain mass campaigns carried out with the assistance of the Organization.[3]

VACCINATION CAMPAIGNS

In 1957 the WHO Expert Committee on Poliomyelitis considered that studies had reached a stage at which large-scale trials in Man were indicated in cases where special epidemiological conditions existed, e.g. where a population was threatened with an epidemic, or in endemic areas where there were signs of a shift to the epidemic form of the disease. The Committee recommended that the vaccines used should have given proof of their harmlessness in laboratory tests on monkeys and should have been tested also on small groups of people. Thus, during the 2 years preceding the large-scale campaigns described below, limited trials were carried out in family groups and children's homes in the United States of America (Louisiana and Minnesota in particular), the Netherlands, Poland, Sweden and the USSR. Then larger groups were vaccinated: 3,000 children in Mexico, about 150,000 in Czechoslovakia, and 200,000 in Singapore. In Louisiana it was found that the transmission of the viruses from vaccinated persons to contacts was much more frequent in groups of persons at a low social and economic level (51% of household contacts infected) than among groups in which hygiene was better (8% infected). Several attenuated vaccines were used, particularly the Sabin, Koprowski and Lederle vaccines.

THE USSR

In 1956 the attenuated Sabin virus was studied in monkeys at the Institute of Virology in Leningrad. In 1957 it was administered to 150 infants and in 1958 to 2,500 children under school age. In view of the strong evidence in favour of its harmlessness and efficacy, the USSR Ministry of Health then authorized general use of the vaccine and by the end of May 1959 it had been administered to several million children in various republics of the USSR. In describing these experiments at the Washington Conference, Smorodintsev and his colleagues emphasized that the vaccine stored in the frozen state at $-12°$ or $-15°$ C is extremely stable and that its activity is maintained at the same level for 1–2 years. The vaccine used contains 100,000 tissue culture infective doses ($TCID_{50}$) per 0.1 ml. It is administered by means of a dropper. The vaccination schedule consists of the consecutive administration of

virus types 1, 3 and 2 at intervals of 3–4 weeks, or of administration in 2 stages: first type 1, then a month later types 2 and 3. Under these conditions the percentage of serological reactions to type 1 is 95, to type 2, 80, and to type 3, 75. If under this schedule the antibody titre falls after a time to an unsatisfactory level, the 3 types of virus can be administered again a year later.

The viruses multiply well in the intestines and reach high concentrations in children without antibodies in their blood. They are found in the intestinal contents on the day following administration and reach maximum titres on the seventh to fourteenth day. They may be excreted for as long as 50 days. The intensive reproduction of the viruses and their excretion lead, as explained, to extensive spread of the vaccine virus. In a specific case described by the Soviet workers, 50% of the non-vaccinated contacts had become virus carriers within 30–50 days of the vaccination. In the majority of these virus carriers, contamination by contact had led to antibody formation. The Soviet authors furthermore declared that the most important feature of the live vaccine is its ability to stimulate the development of local immunity in the intestinal canal. Thus, when the same type of virus is administered to vaccinated children 6 months after the primary immunization, it multiplies only to a small extent and slowly. This form of immunity, about which little is yet known, requires further study.

LÉOPOLDVILLE (BELGIAN CONGO)[4]

Paralytic poliomyelitis is endemic and epidemic in Léopoldville. Rodhain studied it there as long ago as 1919. Since 1951 there have been on the average 58 new cases a year —a rate of 18.8 per 100,000 inhabitants. More than 90% of cases have occurred in African children under 3 years of age. Encouraged by the success of vaccination campaigns, which in 1957 covered some 250,000 inhabitants of Ruanda Urundi and other territories in the Belgian Congo, it was decided to vaccinate the most susceptible population group in Léopoldville, i.e. African children under 5 years of age. For various reasons, this city was particularly suitable for testing the harmlessness of the vaccine and for studying the virus. In the Ancienne Cité, 125,000 Africans live in conditions of overcrowding and poor hygiene which favour the passage of the virus from one child to another. Furthermore, 21.7% of the city's African inhabitants fall within the susceptible age group. In addition, the health services and hospitals are excellent and ensure that the results of vaccination are conscientiously assessed. The vaccinations were carried out in community centres, dispensaries, schools or well-baby clinics, or at the Wanson Institute, where every inhabitant of Léopoldville has to undergo an annual examination for sleeping sickness, tuberculosis, leprosy and venereal diseases.

The vaccine used consisted of attenuated viruses of Koprowski's CHAT strain. The virus on which this vaccine is based comes from the fourth human passage of a virus pool of type 1 (SM). The faeces were passaged on monkey kidney culture, and then certain plaques (cytopathological lesions caused by the virus as it develops in colonies on the tissue culture) were again given several passages in tissue culture. The viruses thus obtained were remarkably attenuated, as was indicated by their lack of intracerebral and intraspinal pathogenicity.

Blood specimens were taken before and after vaccination in order to establish the percentage of children susceptible to type 1 and to all 3 types. By the end of April 1959 almost 46,000 children had been vaccinated, and about 1 in 5 of them had been re-examined 8–15 days after vaccination in a vaccination centre or by visiting nurses. None of the cases of illness reported among these children in the weeks following vaccination was either paralytic poliomyelitis or aseptic meningitis. Poliomyelitis was also excluded as the cause of an acute encephalitis which occurred in a vaccinated child.

The vaccination campaign had been under way for 2 months when an epidemic of paralytic poliomyelitis broke out in Léopoldville with 99 cases and 4 deaths, i.e. a morbidity rate of 28.6 per 100,000 (344 per 100,000 for 1-year-olds). As in previous epidemics, 90% of the cases were in the age group 3 years and under. Eighty-nine of the cases occurred in non-vaccinated children. The distribution of the cases by age group was the same as in previous epidemics but, in contrast to the usual picture, cases were relatively less frequent in the Ancienne Cité. The figures are too small to furnish statistical proof of the effect of vaccination. It is not unreasonable, however, to assume that it was important, although it is possible that some unknown epidemiological factor played a part. The hypothesis of the vaccination having caused the disease in two cases in which the incubation period made this a possibility, did not, accord-

ing to the authors, stand up to serological and genetic analysis, which showed that the pathogenic viruses were different from the CHAT virus.

To the surprise of the investigators the serological reaction was positive only in 60% of those vaccinated in Léopoldville, whereas in other limited population groups in the United States and Poland the serological efficacy of the CHAT strain was 90–95%. Negligence and faulty administration can be ruled out and the most plausible explanation seems to be that given by various authors who have observed similar results in regions where hygiene is not at a high level, i.e. probable interference with the poliomyelitis vaccine virus by 'wild' enteroviruses normally present in the intestines of the vaccinated persons. At Léopoldville such competition between viruses seems probable, to judge from the investigation recently made there by Vandeputte,[5] who isolated enteric viruses from 37% of 1,200 faeces specimens obtained during a single year from African children under 5 years of age, who were subject to epidemics of virus diarrhoea.

This phenomenon of interference between viruses contributes to a paradoxical situation in poliomyelitis protection. In environments where hygiene is at a high level and overcrowding rare, i.e. where the risks of mutual contamination are lowest, the children are not naturally protected by subclinical infections occurring when they are young, and remain dangerously susceptible to the virus. On the other hand, in communities where hygiene is rudimentary and where children contract subclinical infections at an early age and are carriers of enteric viruses, the latter can prevent effective antipoliomyelitis vaccination and hinder the formation of protective antibodies.

ANDES (COLOMBIA)

In Colombia paralytic poliomyelitis is a disease of scarcely more than minor public health importance. The highest incidence reported was 1.6 per 100,000 inhabitants in 1953. While the paralytic form of the disease is rare, poliovirus infection seems to be very widespread in certain regions of the country, to judge from the antibody level observed from the age of 2 years onwards. In the 7– to 9-year-old age group, 88% of the children have antibodies to the 3 types of virus, a phenomenon which occurs in other areas of the world with similar social and economic conditions.

In January 1958 cases of paralytic poliomyelitis were reported from the municipality of Andes in the State of Antioquia, in a commune which was partly urban and partly rural, situated in a mountainous area between 1,000 and 3,000 metres above sea level. The fear of a shift from the endemic to the epidemic form of infection impelled the authorities to undertake a campaign of vaccination with attenuated virus with the aid of the Pan American Sanitary Bureau, which serves as the WHO Regional Office for the Americas. The vaccine used was of the same strain as that which had given satisfactory and reassuring results among small groups in Minnesota. More than 7,000 children were vaccinated with 3 successive oral doses of the 3 types of vaccine. Of the children serologically negative to the 3 types before vaccination, 91% responded to the administration of type 1, 72% to type 2 and 87% to type 3. Among those with poliomyelitis antibodies already in the blood, the vaccine had a booster effect, quadrupling the original antibody titre. The few cases of poliomyelitis reported in Andes since the campaign have not been among vaccinated children and no untoward side effects have been recorded.

It is interesting to compare the virulence of the virus used for the vaccine with that of the poliovirus causing one of the paralytic cases which led to the fear of an epidemic. While 2 $TCID_{50}$ of the pathogenic virus paralysed an intracerebrally infected monkey, more than 10 million $TCID_{50}$ of the attenuated vaccinal virus were required to cause the slightest paralytic symptom among monkeys of the same species inoculated by the same route.

POSSIBLE REVERSION OF THE ATTENUATED VIRUSES TO VIRULENCE

Attenuated poliomyelitis viruses obtained in accordance with the principles described are less neurotropic, or non-neurotropic, for the primates, including Man. Neurotropism, however, is not a fixed and immutable quality inherent in a particular poliovirus and transmitted to the strain derived from it. It can show a wide range of variation and depends, moreover, on the susceptibility of the neurones with which it comes in contact. The fact that the inferior motor neurones are more highly resistant in the primates has been established beyond doubt and it seems certain that, the

higher the position in the evolutionary scale, the lower the sensitivity to the poliovirus of the neurones and the higher the sensitivity of the digestive system.

The site of the test inoculation of the monkey where the neurotropic qualities of a virus are being assessed is of great importance and should be specified for comparative tests of the harmlessness of the vaccine, since monkeys show different levels of susceptibility depending on whether an intracerebral injection is made in the thalamic region or an intraspinal injection in the grey matter of the lumbar enlargement of the spinal cord.

A crucial problem arises with regard to the possibility of a reversion of the attenuated virus to virulence. How can the vaccine viruses be differentiated from 'wild' viruses in faecal specimens in the absence of any distinguishing morphological characteristic, even of an ultra-microscopic kind? This question becomes acute:

(*a*) When it is necessary to establish whether an attack of poliomyelitis in a vaccinated person or contact could be due to a mutation of the attenuated virus;

(*b*) If the incidence of poliomyelitis increases in a vaccinated population; and

(*c*) When it is proposed to vaccinate the population during an epidemic.

Sensitive serological methods, based on the inhibiting action of the specific sera of strains on virus cultures in monkey kidney tissue, have been elaborated. The specific serum prevents the formation of plaques in the case of a homologous virus and has no effect in the case of a heterologous virus.[6]

Recourse is also had to what are called genetic methods, using 'markers' which appear to be stable. Among the reference characteristics for poliovirus, the following have been chosen:

1. Plating efficiency under agar of low bicarbonate content;

2. The appearance of the plaques in tissue cultures of fresh monkey kidney and established lines of monkey kidney (the MS character);

3. The ability of the virus to develop or not at a temperature of 40–41°C.

There seems to be a close correlation between the ability of type 1 virus to develop at a high temperature and its neurovirulence. It may even be supposed that these 2 characteristics are genetically identical or very closely related.

As related above, a comparison between epidemic viruses and vaccine viruses proved necessary during the Léopoldville epidemic which broke out during a vaccination campaign. Koprowski *et al.*[7] analysed these 2 viruses and showed that they were different. This analysis confirmed the indications that some characters were inherent in the attenuated forms and the contrary characters in the 'virulent' forms.

ACHIEVEMENTS AND NEEDS

It was the opinion of the Washington Conference that, while the inactivated (Salk) vaccine has proved its value and can be strongly recommended, its use does not preclude that of a less expensive and more easily administered vaccine, which might replace the 'wild' paralytogenic strains in nature by strains with lessened neurotropism. However, the fact (which in itself has certain advantages) that the vaccine virus spreads to contacts is not without its risks, since its spread cannot be controlled. These risks were discussed and assessed at length by the Conference. The neurovirulence of the vaccine virus has hitherto been considered as the factor involving the greatest risk. Other factors, however, also require study: the invasive power of the virus in the organism, viraemia in vaccinated persons, the contagious properties of the virus and its ability to spread from one person to another, its genetic stability, and the value of certain markers as criteria of infectivity permitting differentiation between 'wild' polioviruses and the viruses excreted by vaccinated persons.

It remains difficult to assess the results of vaccination campaigns, particularly if a statistically valid verdict on efficacy is required. Such assessments are at present based above all on qualitative comparisons. The serological response which can be measured in important sample groups of the population has raised the question of the interference of enteric viruses with the poliovirus and of interference between the polioviruses themselves. This is a subject for wider research. The spread of vaccine viruses in communities partially immune before vaccination, which is slower than in non-immune communities, is still a matter for study. However imperfect the trials of the live vaccine made so far, nothing has arisen to suggest that it is not harmless, or to throw doubt on its effectiveness once the organism has responded by producing antibodies and excreting viruses.

LIVE POLIOVIRUS VACCINATION

IN THE USSR, POLAND AND CZECHOSLOVAKIA

Live poliovirus vaccination has already been practised on a large scale in the USSR, Poland and Czechoslovakia. With the agreement of the ministries of health in these 3 countries, WHO invited Dr. Dorothy Horstmann, Associate Professor of Preventive Medicine and Pediatrics at the Yale University School of Medicine, USA, to visit these countries between August and October 1959 and evaluate the results of the mass vaccination programmes carried out with the live vaccine. She spent most of the time at her disposal in the USSR, and a week each in Poland and Czechoslovakia.

THE USSR

Some 15 million persons were vaccinated in the USSR by the end of January 1960, and it is planned to vaccinate another 60 million by the end of the year, i.e. almost the entire population under the age of 20.

Striking features of laboratory work in this country are, in Dr. Horstmann's view, the large staff available and the high standards of sterile technique. The methods used for preparing tissue cultures and for the determination of neutralizing antibodies are similar to those used elsewhere, and the laboratory work is of good quality. Some delay seemed to her to occur in the carrying out of tests, and particularly in the isolation of virus from cases, due mainly to the large number of specimens collected from areas scattered through vast tracts of country and to the absence of staff on expeditions to republics starting vaccination programmes.

The decision to undertake the vaccination programme was delayed for several months pending detailed study of the problem by the Ministry of Health, and when permission to start was given the vaccine was offered to the republics to use or not as they wished. There had been an epidemic of poliomyelitis in Estonia in 1958, and possibly for this reason this republic was the first to ask for the vaccine. The success of the programme in Estonia set off a 'chain reaction' throughout the other republics, and at the time of Dr. Horstmann's report only one republic had not asked for the vaccine.

The vaccine, which is prepared from the 3 strains developed by Sabin, was administered serially to begin with: first type 1, then type 3, then type 2. In Lithuania groups vaccinated serially in this way were compared with groups vaccinated with a triple vaccine either once or twice; and when the preliminary results showed that there was no significant difference in the 2 methods, triple vaccine became the only one used. In Georgia the administration of triple vaccine to children in sweetmeats is being tried.

The vaccination campaign begins by enlisting the cooperation of the doctors and the public. The directors of the programme assemble the doctors and explain the organization of the programme, the role of the doctors, their responsibilities during the campaign and afterwards, and the importance of close surveillance. Radio and television broadcasts, newspapers and posters bring the aims of the campaign before the public to persuade it of the advantages of cooperation. An important town in each region is selected as a centre. To it is sent frozen vaccine, sufficient for several days of vaccination; and from it teams go out daily, carrying the vaccine in iced thermos flasks. In the rural areas these teams each consist of a medical auxiliary with some medical training (called a 'feldscher') and 2 nurses. In the towns teams are set up in schools, nurseries, kindergartens and outpatient departments, and a physician supervises the work of several teams. Data are recorded on every person vaccinated.

This is the system generally used, but there are slight variations between the republics. There are no control groups and no selection of persons for vaccination other than by age, for this is meant to be a mass vaccination programme, not a controlled trial of a new kind of vaccine for poliomyelitis. As in other mass campaigns, an indefinite number of people have been missed, being absent, ill, or reluctant to face vaccination; but this number was reduced by a continuous vaccination programme through the summer of 1959. Accurate population data have made the planning of the campaign much easier.

Before the vaccination began serological surveys were made to determine the immunity status of the population. The children surveyed in the age group 0–3 consisted only of those living in nurseries or staying in them during the day, a group which Dr. Hortsmann does not think representative of the popula-

tion at large. The survey of the age group 4–7 also drew too heavily on children in institutions and in kindergartens. The group 7–14 consisted mainly of schoolchildren, and the adults surveyed were mainly factory workers. This survey work has been held up by difficulties with the colorimetric neutralization test, but these have been overcome.

Surveillance is efficiently carried out. In each area the vaccination teams are also surveillance teams. In Tashkent, for example, where the vaccine was given during an epidemic, every home was visited every 5–6 days from mid-July to mid-September 1959 to check on possible cases. Generally, however, the local paediatrician notifies a case to the area sanitary and epidemiological station, which sends an epidemiologist to the child's home to make a thorough inquiry into the case and its contacts. The Ministry of Health in Moscow has set up a special notification system for cases of poliomyelitis, and all suspicious cases (that is, all with acute infection of the central nervous system) are sent to hospital for confirmation of the diagnosis and treatment. Dr. Horstmann considered that it was most unlikely that any paralytic cases would be missed under this system.

Since there are no controlled trials, the 1959 incidence of poliomyelitis in vaccinated and unvaccinated persons cannot be compared. But the over-all incidence, in comparison with the previous 5 years, showed a marked fall in 1959. Some of the republics attribute part of this fall to vaccination with the Salk vaccine, but this vaccine has not been extensively used.

Dr. Horstmann concludes that the attenuated live vaccines used appear to have been safe, both to those vaccinated and to the communities in which they live, for at least the 6-month period during which surveillance was carried out. The fall in the number of cases suggests that the vaccine is effective, although the absence of a controlled trial makes it difficult to gauge its effectiveness accurately.

POLAND

Until 1951 poliomyelitis was sporadic in Poland, and of little importance. An epidemic occurred in that year, with an attack rate of 12.2 per 100,000, and an epidemic in 1958 had an attack rate of 21 per 100,000. Cases have been confined to the lower age groups: approximately 70% have been in children under 4 years of age, 95% in children under 8.

Vaccination with the Salk vaccine was begun in 1957 and, in 1958, after the epidemic, extended to most children under 7. In October 1958 vaccination with the Koprowski live poliovirus vaccine was begun on a small scale. Mass vaccination with this vaccine was begun in June 1959, and by the time Dr. Horstmann wrote her report nearly a million children had been vaccinated with types 1 and 3. The aim is to vaccinate the entire population with these 2 types, and for the moment to ignore type 2. Children who have had 2 doses of Salk vaccine receive a booster dose of live vaccine.

As in the USSR, the health services are well organized and surveillance efficient. Vaccination is compulsory, and if parents fail to bring their children they are heavily fined. The immunity status of the population is studied before the vaccine is administered. Dr. Horstmann points out that, because the population is relatively small, accurate information should be available soon on the safety and effectiveness of the vaccine.

CZECHOSLOVAKIA

In 1957-1958 vaccination was extensively carried out, Salk vaccine being used. Sabin live vaccine has now been given to children who had 3 doses of Salk vaccine, and the trial is being well controlled. The standard of work in the laboratories in Czechoslovakia is high, epidemiological services are good, and surveillance is being carefully carried out. The incidence of poliomyelitis was extremely low in 1959.

Serological surveys were made before and after vaccination with the Salk vaccine, and before vaccination with the Sabin vaccine; and the series is being completed with a post-Sabin survey. The prevalence of poliovirus infection is assessed at intervals of 3–4 months by sampling the population under 5 years of age in both vaccinated and non-vaccinated areas. The results from the samples taken 5½ months after vaccination with the oral vaccine show that there is no significant difference between the amount of poliovirus circulating in the vaccinated regions and that in the rest of the country.

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3. Bull. Wld. Hlth. Org., 1960, **22**, 197.
4. Bull. Wld. Hlth. Org., 1960, **22**, 203.
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HIDDEN CONTACTS WITH PENICILLIN

There is already a vast literature on the dangers of the indiscriminate use of antibiotics for therapeutic purposes. Less well known are the possibilities of accidents in persons who have become sensitive to antibiotics to which they have found themselves exposed without even realizing it. These 'hidden contacts' (as they are termed by Bernard B. Siegel, of the Allergy Division of the Department of Medicine, Jewish Hospital of Brooklyn, U.S.A.) are particularly common with penicillin, and are discussed in an article by Dr. Siegel recently published in the WHO *Bulletin*.[1]

One of Dr. Siegel's examples is of a physician who had previously experienced a severe reaction after an injection of penicillin, and who collapsed after drinking a glass of milk, emergency measures being required to bring him out of a state of shock. Later he experienced several other, though less severe, reactions, immediately after drinking milk. Penicillin is much used in the U.S.A. for the treatment of cow mastitis, and has frequently been found in cow's milk in quantities sufficient to provoke allergic reactions in people who are sensitive to it.

Another example is that of a nurse who had become sensitive to penicillin after several intramuscular injections. Later she was given an injection of testosterone with procaine hydrochloride for menstrual irregularity, and within a short time developed pruritus, itching of the throat, and generalized urticaria and angioneurotic oedema. Investigations showed that she was not sensitive to either the testosterone or the procaine, but had reacted to traces of penicillin left in the syringe. This girl had to give up nursing because she had itching of the eyes, nose and throat, swelling of the lips, and tightness of the chest whenever either she handled penicillin or it was used in her presence.

A third example is that of a drug salesman who had experienced severe allergic shock immediately after taking a dose of medicine containing penicillin. A month later, while waiting in a doctor's consulting room, he suddenly started to develop the same symptoms, at a time, it was discovered, when penicillin aerosol treatment was being given elsewhere in the consulting room.

Generally sources of contact with penicillin are obvious, but these examples show that they may also be hidden. Another important hidden source is virus vaccines, which contain small amounts of penicillin antigen sufficient in some persons to cause allergic reactions. In view of the many hidden sources—Dr. Siegel remarks—it would indeed be unwise to assume that anyone living in a modern community can escape contact with this antibiotic in one form or another. But because of the large numbers of potentially sensitive persons, the greatest care should be taken to make this contact as slight as possible.

REFERENCE

1. Bull. Wld. Hlth. Org., 1959, **21**, 703.

THE SOUTH AFRICAN MEDICAL AND DENTAL COUNCIL

REGULATIONS FOR THE REGISTRATION, ETC. OF MEDICAL AND DENTAL STUDENTS*

His Excellency the Governor-General has been pleased, under the powers vested in him by section *twenty-five* of the Medical, Dental and Pharmacy Act, 1928 (Act No. 13 of 1928), as amended, read with sub-section (1) of section *ninety-four* of the said Act, and after considering a recommendation by the South African Medical and Dental Council, to substitute the following regulations for the registration, etc., of medical and dental students under the Act, for the regulations published under Government Notice No. 1083 of 1942, as amended, from time to time:

The regulations are divided into chapters, which relate to the following matters respectively:

Chapter I.—Registration of Medical and Dental Students.

Chapter II.—Minimum Medical Curriculum.

Chapter III,—Professional Examinations relating to Medical Practitioners.

Chapter IV.—Registration as an Intern or a Medical Practitioner.

Chapter V.—Minimum Dental Curriculum.

Chapter VI.—Professional Examinations relating to Dentists.

Chapter VII.—Registration as a Dentist.

* *Government Gazette* No. 1252 dated 14 August 1959.

CHAPTER II

MINIMUM MEDICAL CURRICULUM

The aim of undergraduate medical education must be to train medical students so that after graduation they will be qualified to give maximum service to the community. With this aim in mind, the general trends of the curriculum must be towards satisfying the needs of the future practitioner. The emphasis of teaching should be on instruction in fundamental principles and fundamental methods, rather than informing the students of purely factual knowledge, much of which may be outdated in a short period of time. A student must be given a scientific foundation for his clinical work and must be conditioned towards adapting his professional practice to the ever changing pattern of medical practice. There should be as close integration as is practicable between all subjects taught in the curriculum. He must be taught that the maintenance and promotion of health both of the individual and of the community is as important as the knowledge and cure of illness both mental and physical. He must be taught to observe accurately at the bedside, in the laboratory and by other means, in order that he may by all available means, arrive at reasonable deductions regarding diagnosis, prognosis and treatment. He should at all times be taught to be critical of new and old knowledge, in the furtherance of which objective he should receive instruction in the science of statistics. In order to maintain and promote the health of future generations in the atomic age, he must be taught the principles of genetics, particularly an understanding of the dangers to man of nuclear and allied radiations.

REGULATIONS

1. The period of professional study between the date of commencement of such study, as shown on the certificate of registration as a medical student, and the date of completion of the final professional examination, for any degree, diploma or certificate which entitled its holder to be registered as an intern or medical practitioner, shall be a period of certified study of not less than five academic years, during at least the last three years of which clinical subjects shall be studied in a hospital or hospitals attached to a medical school recognized by the Council.

2. Each university or medical school must make adequate arrangements for the effective correlation of the several subjects of study throughout its curriculum. The actual allocation of parts of subjects between the different departments may be left within the discretion of the universities. Instruction in the basic sciences of Anatomy, Physiology and Pathology should continue throughout the clinical years and must be correlated with the clinical teaching.

3. The course of study prior to registration as a medical student shall take place at a university, shall be so designed as to include instruction in the basic principles which will subsequently be required in the study of all subjects of the medical curriculum, and shall include practical instruction in the following subjects:

A. *Chemistry.* The course shall extend over a minimum of one academic year, and shall include organic chemistry.

B. *Physics.* The course shall extend over a minimum of one academic year.

C. *Zoology and Botany.* These courses shall each extend over a minimum period of half an academic year, or could be combined into a course of *Biological Sciences,* which latter shall extend over a minimum period of one academic year.

4. The course of study for the first two years after registration as a medical student shall be devoted mainly to the following:

A. *Human Anatomy and Physiology.* The course in Anatomy and the course in Physiology shall each extend over a minimum of one academic year and shall include:

(*a*) The study of gross Human Anatomy with adequate experience of dissection of the human body, and the demonstration of the anatomy of the living body;

(*b*) Human Physiology, including experimental physiology, physiological chemistry and nutrition;

(*c*) Histology;

(*d*) Elements of Human Embryology.

Note. The inter-relation of structure and function must be emphasized.

B. The elements of Normal Psychology in its application to physical and mental health.

C. *Pathology.* This course shall extend over a minimum of one academic year and shall consist of:

(*a*) Systematic instruction and practical work on general pathology including morbid anatomy and morbid histology; and in addition witnessing an adequate number of post-mortem examinations;

(*b*) Instruction in medical microbiology and parasitology;

(*c*) Instruction in chemical pathology. The study of chemical pathology in its relation to disease should occur mainly in the years of clinical study.

D. *Pharmacology.* This course shall extend over a minimum of half an academic year, and shall consist of systematic instruction and practical work on the chemical and physical properties of the important drugs, their pharmacological actions, and their main therapeutic applications, and practical dispensing and prescription writing, and shall be closely integrated with the courses in Physiology and Medicine.

5. The final three years of the curriculum shall be devoted mainly to the study of Medicine, Surgery, Obstetrics and Gynaecology and the subjects related and ancillary to these main subjects, and shall include instruction in Applied Anatomy, Physiology, and Pathology. It will be the responsibility of the university to ensure that the teaching programme in those subjects which, for the purpose of the undergraduate medical curriculum are hereunder in paragraph 5D defined as ancillary, is co-ordinated with those of the main clinical subjects.

A. *Medicine.* This course shall consist of:

(*a*) Systematic and practical instruction extending over not less than two academic years in the principles and practice of Medicine;

(*b*) A medical clinical clerkship in the wards of a hospital or hospitals attached to a medical school for a period of not less than one academic year. Instruction shall also take place on out-patients;

(*c*) Instruction in clinical therapeutics and preventive methods.

B. *Surgery.* This course shall consist of:

(*a*) Systematic instruction extending over not less than two academic years in the principles and practice of Surgery;

(*b*) A surgical clinical clerkship in a hospital or hospitals attached to a medical school for a period of not less than one academic year. Instruction shall also take place on out-patients;

(*c*) Practical instruction in surgical methods, particularly in the diagnosis and treatment of the more common surgical diseases and injuries.

C. *Obstetrics and Gynaecology. General Note:* Approximately two thirds of the student's time of the course in Obstetrics and Gynaecology must be given to midwifery, and ante-natal and post-natal work. The course shall consist of the following:

(*a*) Systematic and practical instruction extending over not less than one academic year, on both in-patients and out-patients in the principles and practice of Obstetrics and Gynaecology;

(*b*) An obstetrical and gynaecological clinical clerkship for a period of not less than one year in the obstetrical and gynaecological wards of a hospital or hospitals attached to a medical school;

(*c*) The preventive aspects in infantile complaints should be taught in correlation with the teaching of diseases of children;

(*d*) Every student shall during the course in Obstetrics, personally deliver an adequate number of cases.

D. *Related Special Subjects.* The syllabus of each of the related special subjects: Child health; acute infections diseases; diseases of the skin; anaesthetics; radiodiagnosis and radiotherapy with emphasis on the use and hazards of ionizing radiations; diseases of the eye; diseases of the ear, nose and throat; urology; thoracic surgery; neuro-surgery; orthopaedics, physical medicine, and any other subjects, shall be approved by the university, and the instruction in these subjects shall be integrated by the Heads of the Departments of Medicine and Surgery into the theoretical and practical teaching in these two subjects.

6. *Instruction in Additional Subjects.* In addition to the subjects specified hereinbefore, there shall be instruction in the undernoted subjects; such instruction may be given in any year of study subsequent to the second year of study after registration as a medical student.

A. *Preventive and Promotive Medicine.* This course shall include practical instruction and demonstrations, and should be closely integrated with the teaching in the clinical subjects.

B. *Psychological Medicine.* This course shall extend over not less than one academic year of systematic instruction. Clinical instruction must be carried out in State Mental Hospitals, General Hospitals, and in special hospitals for psychoneuroses (if available), on in-patients and out-patients, and should be closely integrated with the teaching in the other clinical subjects.

C. *Forensic Medicine and Toxicology.* This course shall consist of systematic instruction, and practical demonstrations in the examination of the dead body and medico-legal specimens and materials. Instruction on the clinical

aspects of Forensic Medicine and Toxicology should be carried out in the medical, surgical and obstetrical and gynaecological wards and casualty departments of the teaching hospitals.

D. *Legal and Ethical Obligations of Registered Interns and Medical Practitioners.* Instruction shall be given in the statutory obligations of medical practitioners and interns in the conduct of practice, and in the principles of medical ethics as required by the South African Medical and Dental Council; instruction in these aspects of practice should be closely integrated with all instruction in the curriculum.

CHAPTER III

Whilst it is required that the undermentioned regulations concerning examinations be complied with, Council draws attention to the necessity of continuing during the clinical years of training with instruction in the basic subjects of Anatomy, Physiology, and Pathology as applied to clinical practice. The examinations presented hereunder are considered essential, but must not permit interference with the integration of non-clinical with clinical subjects.

1. The examinations leading to the degree in Medicine shall include examinations in the following subjects:

Group A
- Chemistry;
- Physics;
- Zoology;
- Botany;
- or, instead of Botany and Zoology, Biological Sciences.

Group B.
- Anatomy;
- Physiology;
- Pathology;
- Pharmacology;
- Psychological Medicine;
- Preventive and Promotive Medicine;
- Forensic Medicine and Toxicology.

Group C.
- Medicine;
- Surgery;
- Obstetrics and Gynaecology.

2. The examinations in the subjects enumerated in Group A of regulation 1, shall be written and practical, and at the discretion of the examiners, oral.

The examinations in the subjects enumerated in Group B of regulation 1, shall be written and oral and wherever possible practical.

The examinations in the subjects enumerated in Group C of regulation 1, shall be written, oral and clinical.

In respect of the subject of Psychology as listed in regulation 4B, and the ancillary subjects enumerated in regulation 5D, Chapter II, a teaching institution must satisfy itself of the proficiency of the candidates by such certificates of performance or examinations as are deemed necessary, it being understood that the final examinations may include examinations within the scope of these subjects in their relationship to Medicine, Surgery, and Obstetrics and Gynaecology.

3. Each examination shall be conducted by at least two examiners, one of whom has not taken part in the teaching of the subject to the candidates.

4. Except in the case of subjects of Group A in which the pass mark will be 40 per cent, no candidate shall be considered to have passed in an examination in any subject unless he obtains at least 50 per cent of the maximum marks obtainable in the examinations. Examiners may take into account the duly documented records of work done by a candidate throughout the course of study leading up to the examinations.

5. The prescribed subjects of the examinations may be grouped or distributed at the discretion of the university, provided that the examinations held at the end of the course (the final qualifying examinations leading to the degree) shall include examinations in the subjects enumerated in Group C of regulation 1. No candidate should be allowed to pass who fails in the clinical examination in these subjects.

6. No candidate shall be admitted to the degree in Medicine and Surgery qualifying him for registration until

(*a*) He has completed at least five years of study as a registered medical student;

(*b*) He has passed in examinations in all the subjects enumerated in regulation 1;

(*c*) He has satisfied the examination authorities that he has complied with these regulations.

7. A candidate who fails in any subject of the final qualifying examination shall be required to produce satisfactory evidence that he has pursued the study of that subject during the period between such failure and re-admission to examination.

8. If a candidate does not pass in all the subjects of the final qualifying examination

he may be exempted from re-examination in any subject, provided that he attained a standard which the examiners consider warrants such exemption. Such exemption shall lapse when the candidate fails the other subject or subjects on two successive attempts following the first failure.

NOTE. Attention is drawn to the Regulations Regarding Examinations Conducted at Medical and Dental Schools (Government Notice No. 1637 of 15 December 1932), and the Rules for the Inspection of Examinations at Medical and Dental Schools in the Union of South Africa (Government Notice No. 720 of 31 March 1950), as also to section *twenty-six* and section *ninety-three* (*bis*) of the Medical, Dental and Pharmacy Act, 1928 (Act No. 13 of 1928) as amended.

TWO ORAL DIURETICS IN HYPERTENSION

A COMPARISON OF THEIR POTENTIATING ACTION

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A comparison of the effect of chlorothiazide and hydroflumethazide ('Hydol') was made on the blood pressures of a group of hypertensive patients. In some of these subjects the effect of replacing the diuretic drug by a placebo was assessed. Observations were also made on the effect of these oral diuretic drugs on the serum potassium and the blood urea levels found during and after therapy.

MATERIAL AND METHODS

A group of 18 hypertensive, ambulatory patients were examined weekly for 3–4 weeks while under treatment with chlorothiazide and other hypotensive drugs (mecamylamine, reserpine and hydralazine). Following this control period, chlorothiazide was replaced by hydroflumethazide, while the other hypotensive drugs used in the control period were continued. In each instance, 50 mg. of hydroflumethazide replaced 500 mg. of chlorothiazide and, where the dosage was greater than 500 mg. of the latter drug, proportional amounts of hydroflumethazide were given. Each patient was again followed for a period of 3–4 weeks.

In those patients in whom the blood pressure rose when chlorothiazide was replaced by hydroflumethazide, the dosage of the latter drug was increased by 50% and observations were continued for a further 3–4 weeks.

In 12 of the 18 patients a lactose placebo was given in place of hydroflumethazide and the effects were observed for a period of 3–4 weeks.

Potassium supplements (3 g. daily) were given to all the patients during the period on diuretics, and serum potassium levels were measured at the end of each period of therapy.

Blood pressures were measured after 5 minutes of rest in the supine position and while standing. The body weight and the blood urea level were measured at the end of each period of observation, no patient having a blood urea level greater than 70 mg. per 100 ml. at the beginning of the study.

RESULTS

The replacement of chlorothiazide by hydroflumethazide in a proportion of 10 : 1, showed no statistical difference in the blood pressure levels (Annexure1, Table 1). However, a tendency was found for the blood pressure on hydroflumethazide to be slightly higher than that which was found when the patients were on chlorothiazide. In 6 of the 18 patients in whom such changes were found, an increase of the hydroflumethazide by 50% produced almost identical blood pressures to those which were present during the control period on chlorothiazide. It would appear from these results that chlorothiazide is approximately equivalent

ANNEXURE 1

TABLE 1

THE MEAN SYSTOLIC AND DIASTOLIC BLOOD PRESSURES, BOTH LYING AND STANDING, IN THE CONTROL PERIOD WERE COMPARED WITH THOSE IN THE 'HYDOL' AND PLACEBO PERIOD. P VALUES USING THE 't' TEST ARE GIVEN FOR THE DIFFERENCES OF THE MEANS IN EACH PERIOD.

	1. Period on Chlorothiazide				*2. Period on 'Hydol'*				*3. Period on Placebo*				*Increased Dose of 'Hydol'*				
	Lying		*Standing*		*Lying*		*Standing*		*Lying*		*Standing*		*Lying*		*Standing*		
Case No.	*Systolic*	*Diastolic*	*Systolic*	*Diastolic*	*Systolic*	*Diastolic*	*Systolic*	*Diastolic*	*Systolic*	*Diastolic*	*Systolic*	*Diastolic*	*Systolic*	*Diastolic*	*Systolic*	*Diastolic*	*Control Therapy**
1.	140	97	110	88	160	96	150	79	170	100	150	96	—	—	—	—	Chlorothiazide 500 mg. daily Reserpine 1 mg. *bd.*
2.	158	98	162	98	160	98	160	96	160	98	158	94	—	—	—	—	Chlorothiazide 500 mg. *bd.* Reserpine 1 mg. *tds.*
3.	133	103	115	92	135	97	121	90	175	115	145	108	—	—	—	—	Chlorothiazide 500 mg. *bd.* Reserpine 1 mg. sympathectomized
4.	169	94	146	88	195	99	166	94	—	—	—	—	—	—	—	—	Chlorothiazide 500 mg. daily Reserpine 1 mg. *bd.*
5.	137	89	128	86	150	95	143	91	155	97	133	98	—	—	—	—	Chlorothiazide 500 mg. daily Mecamylamine 5 mg. *tds.*
6.	175	115	150	105	210	140	200	138	—	—	—	—	—	—	—	—	Chlorothiazide 500 mg. daily Mecamylamine 10 mg. *tds.*
7.	160	109	130	90	182	109	162	101	170	110	160	100	170	98	130	88	Chlorothiazide 500 mg. *bd.* Reserpine 1 mg. *bd.* Mecamylamine 5 mg. *tds.*
8.	170	135	136	95	190	126	135	94	211	125	178	121	190	130	120	94	Chlorothiazide 500 mg. daily Hydralazine 20 mg. *tds.* Mecamylamine 10 mg. *tds.* sympathectomized
9.	152	86	141	74	146	86	140	76	158	86	146	80	—	—	—	—	Chlorothiazide 500 mg. daily Reserpine 1 mg. *bd.* Mecamylamine 5 mg. *tds.*
10.	150	107	135	93	160	100	125	88	—	—	—	—	—	—	—	—	Chlorothiazide 500 mg. daily Hydralazine 50 mg. *bd.* Mecamylamine 10 mg. *bd.*
11.	147	95	152	94	147	95	154	92	160	102	156	98	—	—	—	—	Chlorothiazide 500 mg. daily Reserpine 0·1 mg. *tds.*
12.	157	92	150	78	210	100	170	90	190	140	180	126	150	98	140	88	Chlorothiazide 500 mg. daily Mecamylamine 5 mg. *bd.*
13.	152	92	148	92	150	94	148	92	—	—	—	—	120	90	122	92	Chlorothiazide 500 mg. daily Reserpine 0·1 mg. *bd.* Hydralazine 50 mg. *tds.*
14.	180	99	130	92	170	108	158	100	210	120	216	118	164	104	164	98	Chlorothiazide 500 mg. daily Mecamylamine 7·5 mg. *tds.*
15.	160	104	125	97	150	100	130	88	170	100	150	96	—	—	—	—	Chlorothiazide 500 mg. daily Reserpine 0·25 mg. *bd.* Mecamylamine 5 mg. *tds.*
16.	168	112	164	100	183	103	171	97	210	128	198	128	170	100	162	100	Chlorothiazide 500 mg. daily Reserpine 0·1 mg. *bd.* Hydralazine 20 mg. *tds.*
17.	157	114	147	106	175	115	160	106	—	—	—	—	—	—	—	—	Chlorothiazide 500 mg. daily Reserpine 0·1 mg. *bd.* Mecamylamine 5 mg. *bd.*
18.	214	110	201	99	199	112	194	104	—	—	—	—	—	—	—	—	Chlorothiazide 500 mg. *bd.* Reserpine 0·1 mg. *bd.* Hydralazine 20 mg. *tds.*
Means	160	103	137	93	170	104	155	95	178	110	164	105	161	103	139	93	
P Values					·1—·2	·8—·9	·8—·9	·6—·7	·02—·05	·1—·2	·02—·05	·01—·001					

* Potassium supplements (3 g. daily) were given to all patients during the first 2 periods.

to hydroflumethazide in a proportion of 10:1 to 6.6:1 in their hypotensive effects.

The substitution of a placebo for an oral diuretic, while other hypotensive therapy was maintained, produced statistically significant elevation of the blood pressure both at rest and while standing. The effect of the oral diuretic therapy was most marked when comparisons were made between the standing pressures on placebo as against oral diuretic therapy (Annexure 1, Table 1).

The change in the blood urea, serum potassium and body weight was observed during the periods when hydroflumethazide replaced chlorothiazide (Annexure 1, Table 2). An increase in serum potassium was observed when a placebo replaced the oral diuretic, despite the fact that potassium supplements given during the diuretic therapy had been discontinued while the patient received the placebo. These results are highly suggestive that the potassium supplement (3 g. daily) was inadequate to replace the loss caused by the use of oral diuretics.

TABLE 2

Case No.	*Weight Change (lb.)*		*Blood Urea Change (mg. per 100 ml.)*		*Serum Potassium Change (mEq/L.)*	
	Period 1—2	*Period 2—3*	*Period 1—2*	*Period 2—3*	*Period 1—2*	*Period 2—3*
1.	−4	+2	+5	−2	0	+·9
2.	−6	−4	−2	+2	+·1	0
3.	0	+1	0	+4	−·2	−·3
4.	−1	—	0	—	−·4	—
5.	+1	+7	−2	−1	−·4	+·6
6.	0	—	+2	—	−·1	—
7.	0	0	+1	−2	0	+·2
8.	+1	+1	−2	0	+·3	+·1
9.	+1	+3	−4	−1	−·2	+·3
10.	0	—	+5	—	−·3	—
11.	0	+1	+2	−4	+·3	−·1
12.	+2	0	−2	−4	−·2	−·8
13.	−4	—	—	—	—	—
14.	−3	+1	0	−3	−·1	+·4
15.	+3	+1	−8	−1	+·5	+·5
16.	+4	−1	—	—	0	+·1
17.	+1	—	+4	—	0	—
18.	+1	—	+1	—	+·1	—
Mean change	−·2 lb.	+1 lb.	0	−1·1	0	+·3

DISCUSSION

The use of chlorothiazide in hypertension is well established. It has been used alone[7, 8] or as a means of potentiating the action of other hypotensive drugs[2, 10] such as ganglion-blocking drugs, rauwolfia alkaloids and hydralazine.

It has been suggested that its predominant mode of action is to cause a decrease in plasma volume through its natriuretic and diuretic effect.[5] This oligaemia is thought to result in an increase in tone of the vasomotor system, which then becomes more responsive to drugs which block vasomotor function.

A second possible mechanism is that chlorothiazide depletes the body of sodium, thus producing the same effect as a low sodium diet. In view of the fact that the arterial wall has been shown to contain an increased concentration of sodium in hypertension,[10] it is possible that depletion of the latter is related to the fall in blood pressure. The recent demonstration[3] that long continued administration of chlorothiazide results in a decrease in peripheral resistance, may be related to this.

Although hydroflumethazide is active in a far smaller dose than chlorothiazide, there does not appear to be any significant difference in their mode of action or in the maximum rate of sodium excretion of which they are capable.[1, 6, 9] It would not, therefore, be expected that hydroflumethazide would be superior to chlorothiazide in this respect. The present study has shown that it is, in fact, approximately equal in its potentiating effect to chlorothiazide. In the 6 cases where replacement by hydroflumethazide resulted in a rise in blood pressure, an increase in dose produced a fall to the previous level. It is

apparent from this that any differences in response are likely to be due only to differences in dosage. This is compatible with the conclusion of Blagg[1] who, in discussing the diuretic effects of hydroflumethazide, stated that 150 mg. of the latter was about equivalent to 500 mg. of chlorothiazide. Other workers,[6] on the other hand, have noted that hydroflumethazide was 10 times as active as chlorothiazide, dose for dose. There is, therefore, an individual variability in response. The undoubted advantage of hydroflumethazide is its cost, which is approximately half that of chlorothiazide, tablet for tablet.

As a result of therapy with this group of drugs the blood urea may rise mainly as a result of a fall in the rate of glomerular filtration.[4] Taken over the whole group, the absence of change in blood urea level in the first 2 periods would seem to confirm the similarity of effect of the 2 diuretics.

It was interesting to note the increase in serum potassium level after cessation of both diuretic therapy and potassium supplements in period 3. This indicates that the potassium supplements (3 g. daily) were not sufficient to replace what was lost in the urine. It is almost certainly better to use intermittent diuretic therapy while continuing potassium daily.

SUMMARY AND CONCLUSIONS

1. It has been reaffirmed that oral diuretic drugs are effective agents in potentiating the hypotensive action of other drugs (mecamylamine, reserpine and hydralazine).

2. Hydroflumethazide ('Hydol') is as effective in its potentiating hypotensive action as chlorothiazide when proportional dosage is used (chlorothiazide: hydroflumethazide 10:1 to 6.6:1).

3. Both oral diuretic drugs cause a loss of body potassium despite the supplementation of 3 g. daily of potassium during this therapy.

4. Practical implications of this study include the following generalizations:

(*a*) The lower dosage of hydroflumethazide ('Hydol') and its smaller tablet size would make possible its combination with other hypotensive drugs in a single tablet smaller than would be possible with chlorothiazide.

(*b*) The current cost of hydroflumethazide is an important consideration when treatment of hypertension is life-long and added to the use of additional expensive medication.

(*c*) The combination of an oral diuretic with potassium (and other hypotensive drugs) in a single tablet does not appear to safeguard the patient against potassium loss unless additional potassium is supplied.

Thanks are expressed to Prof. G. A. Elliott, in whose Department the work was done, for his encouragement and advice.

The hydroflumethazide ('Hydol') used in this study was kindly supplied by Boots (South Africa).

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NOTES AND NEWS : BERIGTE*

Mr. S. Robert Shar, F.R.C.S. (Eng.), F.R.C.S. (Edin.) has commenced practice as a Surgeon at 230 Lister Building, Jeppe Street, Johannesburg. (*Telephones*: *Rooms*: 22-3822; *Residence*: 44-0228).

* * *

Dr. Louis Hirsowitz, accompanied by his wife Dr. F. Segal, recently left for a 3-month visit overseas.

They will do post-graduate work in England and in Europe. They will be back in Johannesburg at the end of July.

UNIVERSITY OF CAPE TOWN

REFRESHER COURSE FOR GENERAL PRACTITIONERS

18–22 JULY 1960

A Refresher Course for General Practitioners will be held, consisting of lectures, ward rounds and demonstrations in *Medicine, Surgery, Obstetrics* and *Gynaecology and the Specialties* at appointed times between 8 a.m. and 5.30 p.m. daily from 18–22 July. Practitioners who wish to spend a further

three days to attend special clinics, departments, operations etc., are welcome to do so but, unfortunately, will not be able to remain in Medical Residence for this extended period as the students will have returned.

The Course will probably include the following:

A. Ward rounds with senior members of the teaching staff in Medicine, Surgery, Dermatology, Paediatrics, Obstetrics and Gynaecology.

B. Panel discussions by groups of consultants on the following subjects: Bleeding from the Gastro-Intestinal Tract; Common surgical lesions in infants and children; Assessment and Management of Hypertension; Hormones in practice; Acute Trauma —Head, Abdominal and Thoracic; Common Obstetrical and Gynaecological Problems; Psychological Problems in Practice (including Alcoholism).

A feature of these discussions is that ample opportunity will be provided for members of the panel to answer questions raised by the Practitioners attending the Course.

C. Demonstrations by the Consultant staff of the following: Anaesthetic Techniques and Minor Surgery; Minor Gynaecological Procedures; Every Day Orthopaedic Methods.

D. A lecture—demonstration on the following subjects: Care of the Neonate in the first 48 hours; Common Skin Diseases.

E. Sessions *Any Questions*. Special sessions will be provided in General Surgery, Medicine, Ophthalmology and Otorhinolaryngology, Paediatrics and Gynaecology and Obstetrics at which a panel of members will answer questions asked by General Practitioners on any subject not covered by the programme of the Course.

The number of Practitioners that can be accepted for the Course is restricted.

The fee for the Course will be 5 guineas, payable in advance to the Registrar, University of Cape Town. This fee should not be sent until the applicant has been notified that he will be admitted to the Course.

Board and lodging will be available at Medical Residence for those desiring it (and for their wives) at a charge of one guinea per day per person.

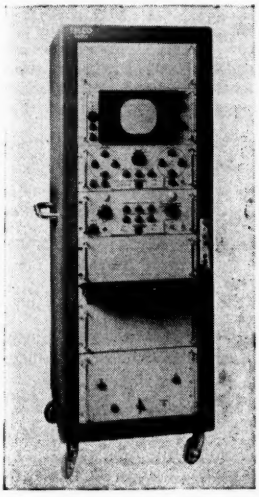
Applications for admission to the Course, stating whether residential accommodation will be required or not, should be submitted as soon as possible to the Registrar, University of Cape Town, Private Bag, Rondebosch.

PREPARATIONS AND APPLIANCES

TELCO ELECTRONIC MEDICAL INSTRUMENTS

Westdene Products (Pty.) Limited announce that they have been appointed the sole importers and distributors for *Telco Electroniaue Medicale et Industrielle*, Paris, France, manufacturers of electronic cardio-vascular diagnostic and survey equipment.

On view in their showrooms at 23 Essanby House, 175 Jeppe Street, Johannesburg, is a rack-mounted unit consisting of the following instruments:



An ECG Amplifier 100% electronically regulated.

A 7-inch persistent screen oscilloscope giving 4 illuminated scales. Speeds 1/2 inch, 1 inch and 2 inches per second.

A 4-channel photographic recorder. The recorder gives automatic markings of time and ordinate lines. Galvanometers from 100 to 700 aps. It uses 120 mm. paper.

The M41 R Electromanometer with its RA 8 transducer head for studying blood pressure by catheterization. The transducer has a multichannel tap and progressive hydraulic damping.

A MM41 R Micromanometer with a minute transducer head fitted to the tip of a No. 8F U.S.C.I. cardiac catheter, used for recording pressure and sound of the heart at the same time. Incorporated in the catheter is a second lumen for blood sampling.

N.B. No artefacts and no liquid column.

A CE4 Four-Channel Electronic switch.

The unit measures:

(*a*) Blood pressure from its standard transducer.
(*b*) Blood pressure from its micro-transducer.
(*c*) Intra-cardiac sound from the micro-transducer.
(*d*) ECG.

The 4 signals are displayed on the 7-inch oscilloscope screen and recorded on a photographic recorder.

For further information regarding Telco electronic equipment or suggestions for equipment for use in a particular field of medicine or surgery, please write to Westdene Products (Pty.) Limited, P.O. Box 7710, Johannesburg, or telephone 23-0314.

ANOREXINE AND DIETING

Anorexine makes dieting easy for the obese patient. Weak moments are almost entirely eliminated, and this regular adherence to the diet which is being followed gives the patient confidence and encouragement.

Anorexine consists of one part laevo-amphetamine with 3 parts dextro-amphetamine, which has been shown to be the optimal formulation for reduction of appetite, while giving a minimum level of central nervous system stimulation quite free from euphoria.

Anorexine produces its unique results through its ion-exchange resin-complex principle which gives completely steady release over a period of 10–14 hours.

Anorexine is available in 3 strengths so that the doctor may prescribe the exact requirements, in a single morning dose, to meet the individual needs of the patient concerned. When deciding on the dose for any particular patient it must be remembered that *Anorexine* affords what is, in effect, depot therapy and that the normal tablet-equivalent will be about one-third of the *Anorexine* content, e.g. a 20 mg. (black) capsule would provide ideal dosage for the patient who requires 1½ standard tablets of amphetamine.

Availability is in bottles of 30 capsules, in the following strengths:

White capsules ... ... 7½ mg.
Black and white capsules ... ... 12½ mg.
Black capsules ... ... 20 mg.

More patients do well on the 12½ mg. (black and white) capsule than on the other sizes.

A bottle of 30 capsules covers a month's treatment. The cost per day averages less than 3d.

Literature, samples and very useful patient diet charts are all available free on application to:

Riker Laboratories Africa (Pty.) Ltd., P.O. Box 3388, Cape Town.

DEGORAN BITABS

Wanders of Switzerland announce the introduction of *Degoran Bitabs* for the symptomatic treatment of coughs, colds and influenza and supply the following information.

Degoran enables treatment of all the symptoms at the same time. It relieves promptly all the distressing manifestations associated with influenza and catarrh. Furthermore, prolonged effect over 6–8 hours is obtained from one *Bitab* (double tablet).

Degoran contains *Triaminic* for its decongestive and secretion-inhibitory effect; Noscapine for its soothing action on the cough reflex; Terpin hydrate, an effective expectorant; and Paracetamol for its quicker antipyretic effect free from the side effects of aspirin. Added to this is the convenience of giving *Degoran* in one *Bitab* which confers the advantages of graduated and timed release of the active principles over a period of 6–8 hours.

Degoran is indicated for coughs, colds, influenza and their associated symptoms—rhinorrhoea, fever, headaches, myalgia, etc. It is supplied in bottles of 24 tablets. The usual dosage for adults is 1 or 2 *Degoran Bitabs* thrice daily and for children (6 to 12 years) 1 to 3 bitabs daily.

Westdene Products (Pty.) Ltd., P.O. Box 7710, Johannesburg, and branches, the sole South African distributors, will be glad to supply literature and samples on application.

SOLCOSERYL FOR PEPTIC ULCERS

Westdene Products (Pty.) Ltd. announce the introduction of *Solcoseryl* manufactured by Solco Basle Ltd. of Switzerland.

Solcoseryl is a completely new treatment for gastric and duodenal ulcers. It consists of a non-albuminous extract of the haemolysed blood of young calves and exerts its effect by increasing cell respiration. The potency of *Solcoseryl* in promoting metabolism is shown particularly in its ability to accelerate the healing of wounds. *Solcoseryl* exerts no bacteriostatic nor antibiotic action.

In addition to peptic ulcers, *Solcoseryl* has also been used in the treatment of myocardial infarcts and leg ulcers. *Solcoseryl* is supplied in 2 c.c. ampoules and the average dosage is one ampoule once or twice daily, given intramuscularly or intravenously. No toxicity or side effects have been reported and there is no possibility of anaphylactic shock because *Solcoseryl* has a molecular weight of only 2,500.

Further information on *Solcoseryl* may be obtained from the sole South African distributors:

Westdene Products (Pty.) Ltd., P.O. Box 7710, Johannesburg.

CORRESPONDENCE

POST-GRADUATE REFRESHER COURSE

To the Editor: Once again we have received a very large number of applications for our intensive post-graduate refresher course, and very much regret that we are unable to accommodate more than 50 doctors, without detracting from our intention of providing a wide range of clinical opportunity and instruction for each member.

We should like to remind practitioners, however, that our next course is being held towards the middle of January 1961, and doctors are asked to apply for that course in good time.

J. Teeger, *Honorary Secretary, Faculty of Medicine/M.G.A. Refresher Course Committee.*

Medical Graduates Association,
University of the Witwatersrand,
Medical School, Hospital Street,
Johannesburg.
Telephone: 44-7040.

ETHICAL RULE RELATING TO CONSULTING ROOMS

To the Editor: As a result of representations made to the Council, it has been giving consideration to a possible amendment of Rule 21 of the Council's Rules Regarding Conduct of which the Council may take Cognisance. The Council invited the views of the Medical Association of South Africa anent the matter, and gave further consideration to the whole matter at its recent 71st Ordinary Meeting.

The Council resolved that the said Rule 21 be not amended, and that the *status quo* be maintained. The Council furthermore directed that all registered practitioners be informed of this decision through the medical press. I shall consequently be pleased if you will be kind enough to direct the attention of practitioners to the above resolution of the Council.

The said Rule 21 of the Rules Regarding Conduct of which the Council may take Cognisance reads as follows:

21. Consulting Rooms.

'1. Having consulting rooms for private practice with the entrance through or with the name plate at the entrance to a chemist's shop.

2. Sharing consulting or waiting rooms with persons not on the medical or dental registers.

3. Using in connection with his consulting rooms the terms hospital, clinic or any other similar name, which might lead the public to believe that the consulting rooms are part of a hospital, clinic, nursing home or other similar institution or have features differing from those of ordinary consulting rooms.

Note: The use on name plates, notepaper or elsewhere of a designation such as Dr. X . . . clinic or hospital, is therefore not permissible.'

W. H. Barnard, *Registrar.*

S.A. Medical and Dental Council,
P.O. Box 205,
Pretoria.